

**MEDICAL FILING REVIEW MEMORANDUM OF ORIGINAL BLA**

**TO: FILE STN: 125325/0**

**See also: STN**

**SPONSOR: KAMADA**

**PRODUCT: ALPHA-1 PROTEINASE INHIBITOR (HUMAN)  
INTRAVENOUS**

**INDICATION: CHRONIC AUGMENTATION AND  
MAINTENANCE THERAPY IN INDIVIDUALS WITH  
CONGENITAL DEFICIENCY OF ALPHA-1 PKLROTEINASE  
INHIBITOR AND CLINICAL EVIDENCE OF EMPHYSEMA**

**FROM: L. ROSS PIERCE, M.D., HFM-392**

**THROUGH: NISHA JAIN, M.D., CHIEF, CRB, HFM-392**

**CC: RPM: Cherie Ward-Peralta**

**SUBJECT: MEDICAL FILING REVIEW OF ORIGINAL BLA,  
REVISED**

**SUBMISSION LETTER DATE: 29 May 2009**

**CBER RECEIPT DATE: 29 May 2009**

**RECOMMENDATION:**

The BLA may be filed with deficiencies 2 through 4 below communicated to the sponsor in writing:

1. Please submit an analysis of the subjects in each treatment group who had the onset of their adverse event (AE) during or within 24 hours of the end of an infusion of study product. For cases in which the time of onset of the AE was not captured, assume that all AEs that began on either the day of an infusion or the day following an infusion occurred within 24 hours of the end of an infusion. Present these data

- (a) only for the initial 12 weeks parallel portion of the study, by treatment group and (b) for the entire duration of study, by actual treatment.
2. Your study report for this study states on p 7 “Two subjects were withdrawn due to AEs, one subject (ID No. -----(b)(6)-----) for pulmonary emboli (Prolastin®) and one subject with urticaria (Kamada-API). The raw dataset for serious adverse events (SAEs) in study -(b)(4)- API 002 (“SERIOU18”) lists 6 SAEs (4 unique AE terms) reported for 4 subjects, all in “GROUP” “API.” GROUP is defined as “Static value of API for every subject.” Please provide the field name in this dataset that indicates to which randomization treatment group each subject belongs.
  3. Why were 2 subjects with AAT phenotype MZ enrolled in study -(b)(4)- API 002, given that this phenotype normally is not associated with serum A1-PI levels  $< \sim 17$  microM?

In addition, please inform the sponsor by telephone that the path in the EDR submission for all SAS transport files (\*.xpt) is incorrect. This prevents the SAS transport files from opening when double clicking them in Global Submit. The sponsor needs to correct this by amendment within 3 business days. In addition, please ask the sponsor to provide the password to permit access to the randomization code Excel spreadsheets, or provide new randomization code Excel spreadsheets which are not password protected.

**Additional letter-ready PMC comment to be communicated later in the review cycle:**

Please conduct a PMC BAL study because of the technical error in BAL sample processing that led to the inability to assess functional A1-PI in ELF.

[This is a very important analyte that was included among the essential endpoints to evaluate A<sub>1</sub>-PI products, as recommended by the joint NHLBI-FDA Workshop held in 1985, which has formed the basis of licensure of all A<sub>1</sub>-PI IV products to date.]

**REVIEW**

**The following deficiencies were communicated to the sponsor by fax dated 16 July 2009. The sponsor's responses from their amendment 02 dated 27 July 2009 are listed in italics below each FDA question, together with my reviewer comments on their reply in bold:**

4. Please redo and resubmit prior to the filing date your adverse events (AE) datasets to include fields for:

- Randomized treatment group
- Product given during the most recent infusion
- Date and start and ending time of most recent infusion
- Date and start time of AE
- Hours elapsed since the end of the most recent infusion (use a value of zero if the AE began during the infusion).

Please include only treatment-emergent AEs in the revised datasets.

***Sponsor Reply:***

*Kamada has updated the existing pivotal study analysis dataset for AEs (i.e., der\_AE) to include fields for those requested by FDA and Treatment Emergent AEs.*

*Since AE start and stop times were not part of the raw database, the following assumption is being made for these values. If an AE began on the day of the infusion and it is not known whether the AE began before or after the start of the infusion, it is assumed that the AE began after the start of the infusion ("worst case") and a value of zero is entered for the number of days from the start of most recent infusion to the onset of the AE.*

**Reviewer Comment:**

**Noted. None of the .xpt datasets open by double clicking on them, due to sponsor error in setting up the path. The dataset was opened with help from Mr. Jeff Smith by manually navigating to the corrected location in Microsoft Explorer and then dragging and dropping the datasets one by one into JMP 7.0. The revised dataset appears acceptable, but it is noted that the sponsor did not capture the starting time of AEs. The sponsor has included a field for the**

**number of days elapsed since the last infusion. If the AE was reported on the day of an infusion, a zero value is given for this variable and it is assumed, conservatively, that the AE began during or after the infusion.**

5. Your define.pdf data definition table for the raw data sets is inadequate in that it does not provide complete and unambiguous definitions of all data fields. Please submit revised definition tables to prior to the filing date to correct this deficiency.

***Sponsor Reply:***

*Revised definition tables for the raw and derived data from the pivotal study (API-002) are included in this submission. An extensive review was performed on the raw datasets to incorporate FDA comments and to provide as much clarity on these fields as possible. Many of the variables have had the labels updated (see file "[List of label changes.xls](#)"). Additionally, several columns were removed from the raw datasets (see file "[List of removed columns.xls](#)") as they existed within the datasets solely for the data collection system purpose and werenot utilized for the analysis (examples include a system generated unique ID number and fields that were used for back-end edit check processing). These changes were applied to the datasets as well as to the Define.PDF. Please note that all the raw and derived data for the pivotal study (API-002) and the SAS program files (including a WORD file "SAS Program Documentation (API-002)" which provided each program description) are being resubmitted with this submission, including those that remained unchanged.*

**Reviewer Comment:**

**Noted.**

6. Neither your raw nor your analysis datasets appear to contain raw data for the primary endpoint analytes, antigenic and functional A<sub>1</sub>-PI from individual sampling time points for either the pivotal trial or the single-dose PK/safety study. Please submit these data prior to the filing date. PK data from each sampling time should be submitted for each subject.

***Sponsor Reply:***

*PK study raw and derived data for the primary endpoint analytes, antigenic and functional A1-PI from individual sampling time points are provided with this submission.*

*Raw data for the primary endpoint analytes, antigenic and functional A1-PI from individual sampling time points for the pivotal study are provided with this submission*

*(for pivotal study API-002 see files "AAT--(b)(4)- WEEK 13-24 V1 9-26-08.xls" and "AAT--(b)(4)- WEEK1-12 V4.xls"; for PK study API-001 see files "pklabdata.xpt ;pkantigenic.xpt ;pkfunctional.xpt").*

*In addition, excel files have been included in the analysis datasets to provide the laboratory data that was collected for the pivotal study.*

*Descriptions for each of these files have been provided within a new defined document (see file "Lab\_XL\_Define.PDF"). Additionally the Derived Define PDF has been linked to this*

*document to provide an easy path for the reviewer to determine how the files were used in the analysis datasets.*

*The raw define.pdf has been updated to reflect this new data. Antigenic and functional API derived data from the pivotal study was previously provided with the original BLA*

**Reviewer Comment:**

**Noted. None of the .xpt SAS transport files open when double clicking them from within Global Submit or from within Microsoft Explorer. The sponsor needs to correct this within 3 business days. The sponsor does not provide in its response the location of the raw A1-PI antigenic and functional serum level data from the single dose PK study. This has been submitted only in .xpt format. The dataset lacks an elapsed time since infusion field, but gives clock times of each sample.**

7. A spot check of your raw datasets indicates that they are inadequate in that, when right mouse clicking on the field names, the column

information dialog box does not provide any additional definition beyond just repeating the field name. The column information for the analysis datasets also appears to be inadequate. For example, “Treatment Number” values of “1” and “2” are not defined and “MAAT” (mean aat”) does not indicate over which weeks trough levels are averaged for this derived variable in dataset “AATP1ITT.” Please re-do and resubmit your datasets by the date mentioned above to correct this deficiency.

***Sponsor Reply:***

*Raw datasets for the pivotal study have been updated to include additional definition information in the column information dialog box. An extensive review was performed on the raw and derived datasets to incorporate FDA comments and to provide as much clarity on these fields as possible. Many of the variables have had the column information for the analysis updated. Additionally, several columns were removed from the raw datasets as explained above in answer to question #2.*

*These changes were applied to the datasets as well as the Define.PDF.*

*Please note that all the data and program files for the pivotal study (API-002) are being resubmitted with this submission, including those that remained unchanged.*

**Reviewer Comment:**

**Noted. As noted above, none of the .xpt datasets opens properly by double clicking on them.**

8. It does not appear that you have submitted any SAS export files for the single dose PK/safety study. Please submit adequate SAS export files for this study prior to the filing date.

***Sponsor Reply:***

*Raw and derived SAS export files for the single dose PK/safety study (API-001) along with define.pdf data definition files, annotated CRF (blankcrf.pdf) and the program files are included in this submission.*

**Reviewer Comment:**

**Noted. As noted above, none of the .xpt datasets open by double clicking on them from Global Submit. In the future, the sponsor should provide the location of all datasets.**

**DEFICIENCIES**

The pivotal phase 2-3 study had only 4 weeks post-end-of-dosing viral follow-up, which is not in keeping with Div. of Hematology current thinking, which requires 6 months follow-up testing for HCV and HIV unless each subject received only a single lot of product.

The statement of the primary endpoint is unclear: “Circulating antigenic **and/or** [emphasis added] functional API trough level averaged over Weeks 7-12 (6 infusions). The goal of this study was to demonstrate that Kamada-API is not clinically inferior to Prolastin®. The definition of lack of inferiority was an average trough value no lower than 3 µM below that of the control product at steady state, as assessed using a 95% confidence interval for the difference in mean values.

“Due to an irreversible technical error accidentally made by the lab technician at the time of BAL sample processing, no results were obtained for functional-API in the BAL samples.”

The proportion of subjects having steady-state functional A<sub>1</sub>-PI (-(b)(4)-) levels < 11 microM was greater for both Kamada A<sub>1</sub>-PI and Prolastin arms (33.3% and 37.5%, respectively) than has been seen in other trials. The reason for this is unclear, but highlights that a substantial proportion of subjects may be underdosed using the recommended 60 mg/kg IV weekly dose, even when using the poorly-supported historical therapeutic trough target level of > 11 microM.

Based on AEs considered by the investigator to be at least possibly product related, Kamada A<sub>1</sub>-PI may be more allergenic than Prolastin. Urticaria,

rash, joint swelling, and thrombocytopenia were reported (1 case each) only in the Kamada arm. This could reflect the small size of the study and the 2:1 randomization.

**The Adverse Events dataset, (ADVERS10.XPT), appears to lack a datafield to indicate to which treatment group the subject has been assigned. It also lacks data to permit calculation of the number of hours/days since the end of the last test product infusion.**

The sponsor cover letter is self-contradictory, in that it states that one clinical study is submitted in support of the application, yet the BLA contains 2 studies:

**Study -(b)(4)- API 001:**

**The pharmacokinetics and safety of an Alpha -1 proteinase inhibitor -(b)(4)--API in subjects with congenital API deficiencies. A dose-escalation clinical trial. (Phase 1)**

N = 18

This study was an open-label single dose escalation safety and PK study testing 30, 60, and 120 mg/kg IV of the test product in subjects with congenital AAT deficiency.

**Robert A. Sandhaus, MD, PhD, FCCP**, Clinical Professor of Medicine, Director, Alpha1-Antitrypsin Deficiency Program, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206

**James. M. Stocks, MD**, Professor of Medicine, The University of Texas Health Center at Tyler, Department of Medical Specialties, 11937 US Highway 271, Tyler, TX 75708-3154

**Mark Brantly, MD**, Professor of Medicine, Molecular Genetics and Microbiology, Alpha One Foundation Research Professor, University of Florida School of Medicine, 1600 SW Archer Road, Room 452 Medical Science Building, Gainesville, FL 32610225



**Gerard Turino, MD**, Senior Professor of Medicine, St. Luke's/Roosevelt Hospital, Department of Medicine, 1000 Tenth Avenue, Suite 3A55, New York, NY 10019

**Study -(b)(4)- API 002:**

**Phase 2/3 Randomized Double-Blind Comparison of Alpha-1 Proteinase Inhibitor (Kamada-API) with Prolastin® in Individuals with Alpha-1 Antitrypsin Deficiency (Phase 2-3)**

**N = 50**

**This study was a 2:1 randomized (test to Prolastin control) 2-arm, randomized, active controlled, double-masked multicenter PK non-inferiority study with a partial crossover. Test and control products were administered IV at 60 mg/kg weekly to subjects with congenital AAT deficiency for 12 weeks. Subjects were then doses another 12 weeks with Kamada A<sub>1</sub>-PI test product only. Lung Epithelial Lining Fluid (ELF) analytes from bronchoalveolar lavage (BAL) that was performed on a subset of subjects at 2 centers were compared between products.**

**Principal Investigator:** Dr Robert Sandhaus

**Other Investigators:** Dr James Stocks, Dr Mark Brantly

**Study Centers:** National Jewish Medical and Research Center (Denver, CO), The University of Texas Health Center at Tyler (Tyler, Texas), and University of Florida School of Medicine (Gainesville, FL).

**Study Dates:** 7 March 2007 to 27 March 2008

**RESULTS OF PHASE 2-3 PK NON-INFERIORITY STUDY -(b)(4)-API 002:**

**DISPOSITION OF SUBJECTS IN PIVOTAL STUDY**

The number of subjects randomized was 52. Two had withdrawn consent and were randomized in error but not dosed. Thirty-three were administered Kamada A<sub>1</sub>-PI and 17 were administered Prolastin. Two subjects were withdrawn early due to AEs (urticaria in the Kamada A<sub>1</sub>-PI group and pulmonary emboli in the Prolastin group). Zero Kamada A<sub>1</sub>-PI and one

Prolastin subject discontinued prior to week 12 (end of randomized, double-blind period).

The number of subjects who completed the 28 week study was 48.

Enrollment was balanced by randomized treatment group across centers with a ~ 2:1 ratio of subjects randomized to the Kamada test product compared to Prolastin at each site.

Thirteen of planned 15 subjects underwent BAL sampling. Of these only 11 had evaluable samples (9 in the Kamada A<sub>1</sub>-PI group and 2 in the Prolastin group).

#### DEMOGRAPHICS IN STUDY -(b)(4)- API 002:

##### Demographics (ITT) (from Sponsor's Table 7)

Parameter	Statistic	Kamada-API N=33	Prolastin® N=17
Age (years)	Mean (SD)	55.4 (7.7)	55.7 (9.2)
	Median	55	55
	Min, Max	42, 72	42, 74
Gender (n,%)		Male 17 (51.5%)	8 (47.1%)
	Female	16 (48.5%)	9 (52.9%)
Race (n,%)	Caucasian	33 (100%)	16 (94.1%)
	Hispanic	0	1 (5.9%)
Height (cm)	Mean (SD)	171.8 (11.0)	172.3 (8.7)
	Median	173	174
	Min, Max	147, 191	154, 188
Weight (kg)	Mean (SD)	82.3 (23.1)	85.7 (17.7)
	Median	81.4	83.6
	Min, Max	40, 162	55, 113

##### Phenotype (from Sponsor's Table 9)

Phenotype	Kamada-API	Prolastin®
(n,%)	N=33	N=17
ZZ	28 (84.8%)	15 (88.2%)

MZ	2 (6.1%)	0
SZ	2 (6.1%)	0
Unknown	1 (3.0%)	2 (11.8%)

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**It is unclear why 2 subjects with phenotype MZ were enrolled in the study, as their serum A<sub>1</sub>-PI levels are normally 17 microM or above.**

## **PROTOCOL VIOLATIONS**

Two subjects (1 per randomization group) were randomized in error.

One subject received exogenous A<sub>1</sub>PI slightly less than the required 5 weeks prior to study start.

In the Kamada product group, 12 subjects missed 1 or more infusions and A<sub>1</sub>PI levels.

In the Prolastin group, 3 subjects missed single infusions and these 3 plus another subject missed having an A<sub>1</sub>PI level drawn.

**A list of protocol violations was reviewed by the sponsor prior to database lock to determine if major violations had occurred which would exclude subjects from an analysis dataset.**

## **EFFICACY**

Mean baseline antigenic A<sub>1</sub>PI levels were 4.8 microM in the Kamada A<sub>1</sub>PI group and 4.3 microM in the Prolastin group. Mean functional A<sub>1</sub>PI levels were 3.1 microM in the Kamada A<sub>1</sub>PI group and 2.3 microM in the Prolastin group.

**The primary endpoint was met for both antigenic and functional A<sub>1</sub>-PI levels in the sponsor's analysis. Mean antigenic and functional A<sub>1</sub>-PI levels in the modified ITT**

**population were greater for the Kamada A<sub>1</sub>-PI than for Prolastin in the sponsor's analysis.**

**Levels of functional A<sub>1</sub>-PI were notably lower in both Kamada A<sub>1</sub>-PI and Prolastin groups than has been seen in other pivotal trials of U.S. licensed A<sub>1</sub>-PI products. This could be due to assay or standard differences, or might reflect sub-potent lots of both products having been used in the study.**

## **SAFETY**

Two subjects were withdrawn prematurely from the study due to adverse events (urticaria in the Kamada A<sub>1</sub>-PI group and pulmonary emboli in the Prolastin group, according to the study report. However, the raw SAE dataset indicated that the subject with pulmonary emboli was in group "A1-PI." The sponsor is asked to clarify this apparent discrepancy.).

- Subject --(b)(6)-- (Prolastin®) discontinued following one dose of study medication due to acute and chronic pulmonary emboli.
- Subject --(b)(6)-- (Kamada-API) discontinued following the Week 12 infusion due to urticaria.

Six SAEs were reported for 4 subjects, all of them in the "API" group. Because pulmonary emboli should be considered a serious AE, it is not clear why this AE which led to premature discontinuation is not listed among the SAEs reported in the trial in dataset, "SERIOU18." The sponsor is asked to explain this.

**AEs considered at least possibly related to the test articles included:**

**Study Period 1 (randomized parallel period – 1<sup>st</sup> 12 weeks):**

**Numbers (%) of subjects reporting Related AEs – study period 1**

<b>AE</b>	<b>Kamada A<sub>1</sub>-PI</b>	<b>Prolastin</b>
<b>Headache</b>	<b>3 (9%)</b>	<b>1 (6%)</b>
<b>Hypertension</b>	<b>1 (3%)</b>	<b>1 (6%)</b>

**Study Period 2 (Open-label weeks 13 – 26):**

**Numbers (%) of subjects reporting Related AEs – study period 2**

<b>AE</b>	<b>Kamada A<sub>1</sub>-PI</b>	<b>Prolastin</b>
<b>Urticaria</b>	<b>1 (3%)</b>	<b>0 (0%)</b>
<b>Dizziness</b>	<b>1 (3%)</b>	<b>0 (0%)</b>
<b>Rash</b>	<b>1 (3%)</b>	<b>0 (0%)</b>
<b>Joint Swelling</b>	<b>1 (1%)</b>	<b>0 (0%)</b>
<b>Decreased Platelet Count</b>	<b>9 (1%)</b>	<b>0 (0%)</b>
<b>Influenza-like illness</b>	<b>9 (1%)</b>	<b>0 (0%)</b>
<b>Lethargy</b>	<b>0 (0%)</b>	<b>1 (6%)</b>

**No subjects seroconverted for HBV, HCV, or HIV during the study.**